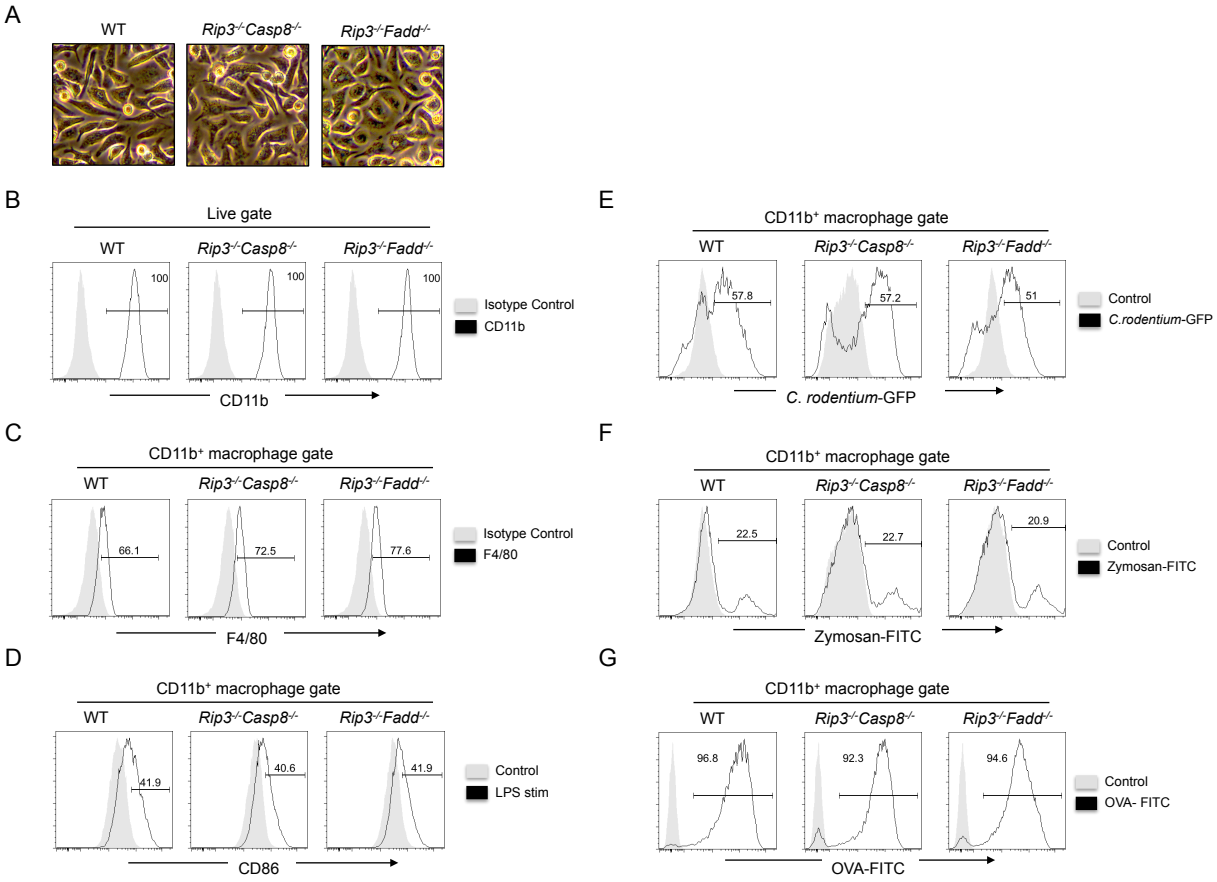
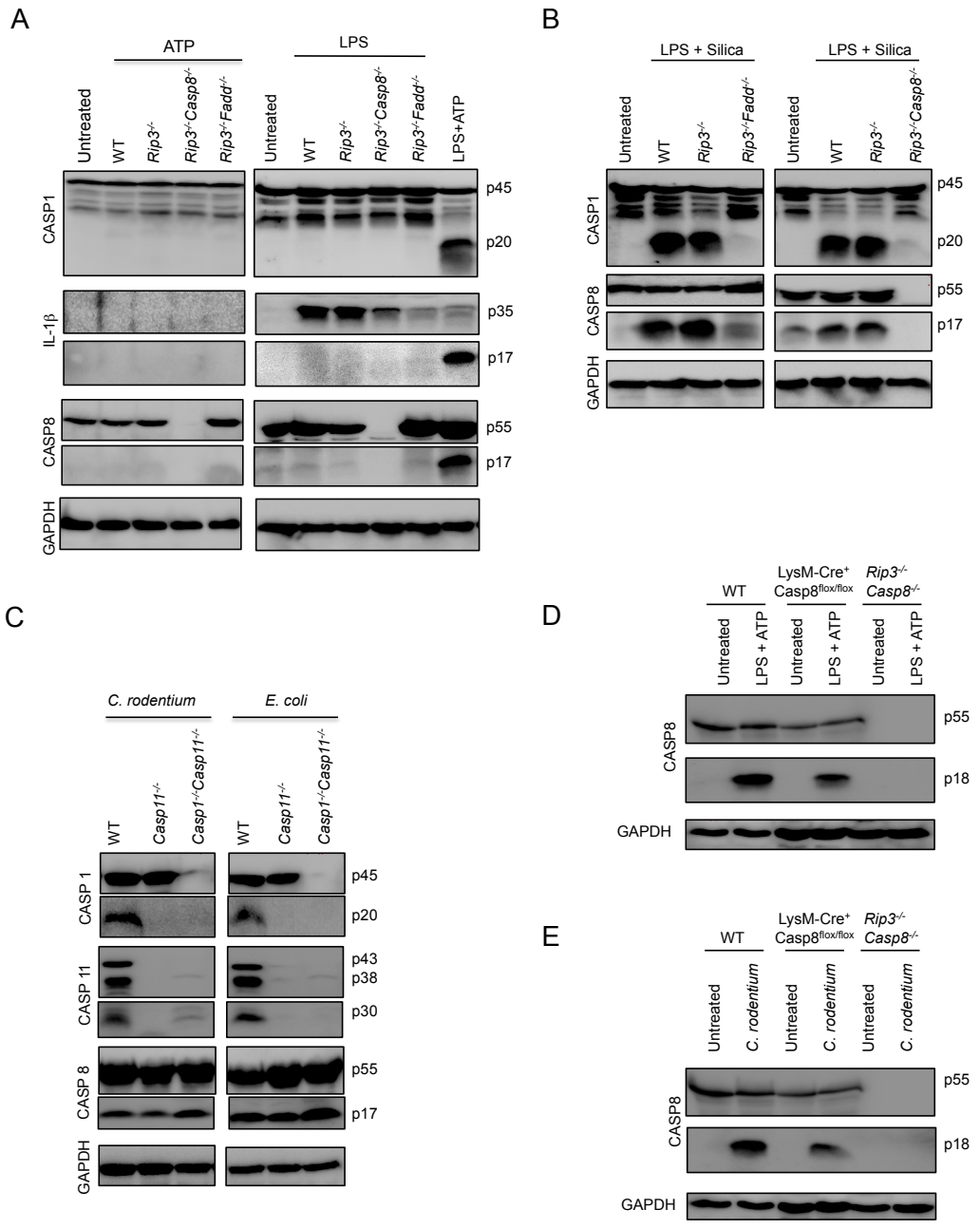
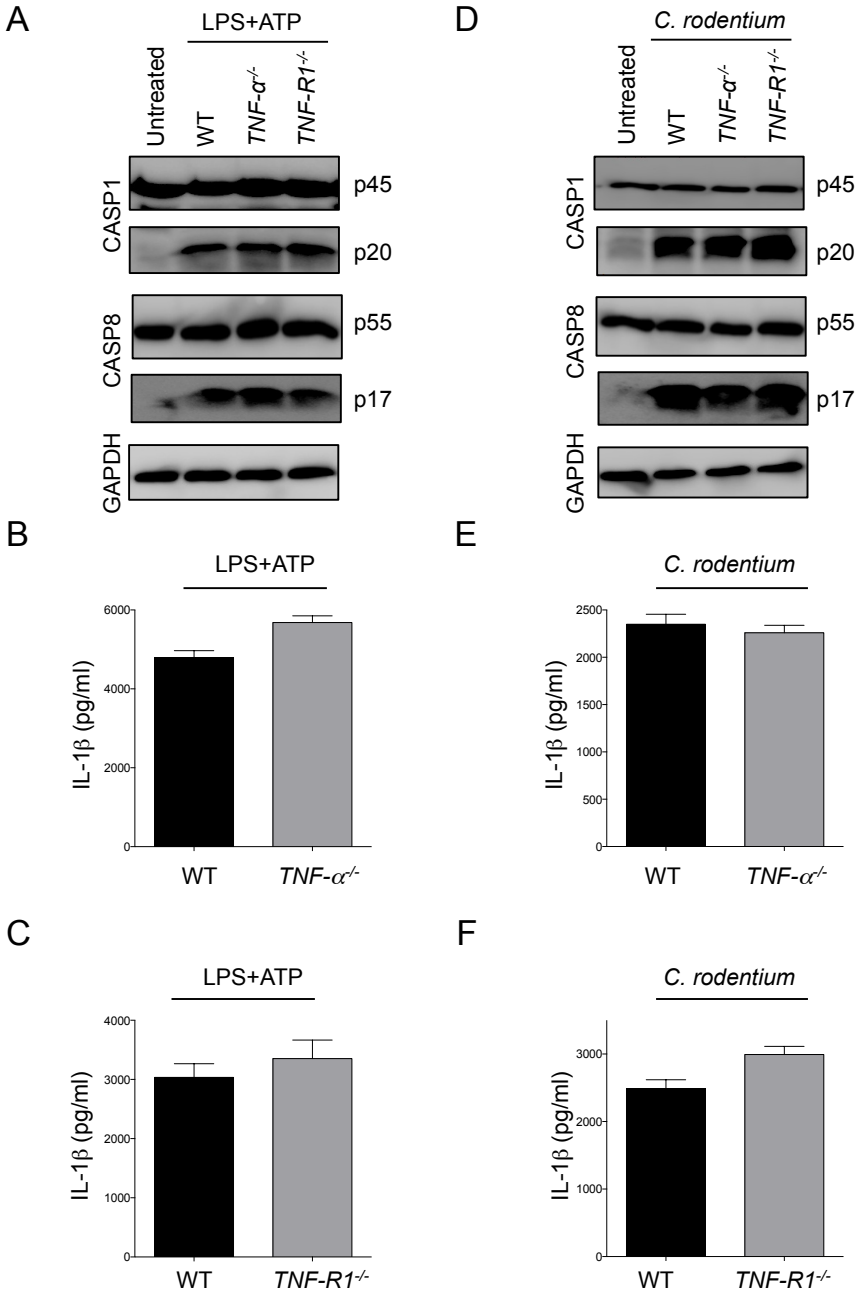


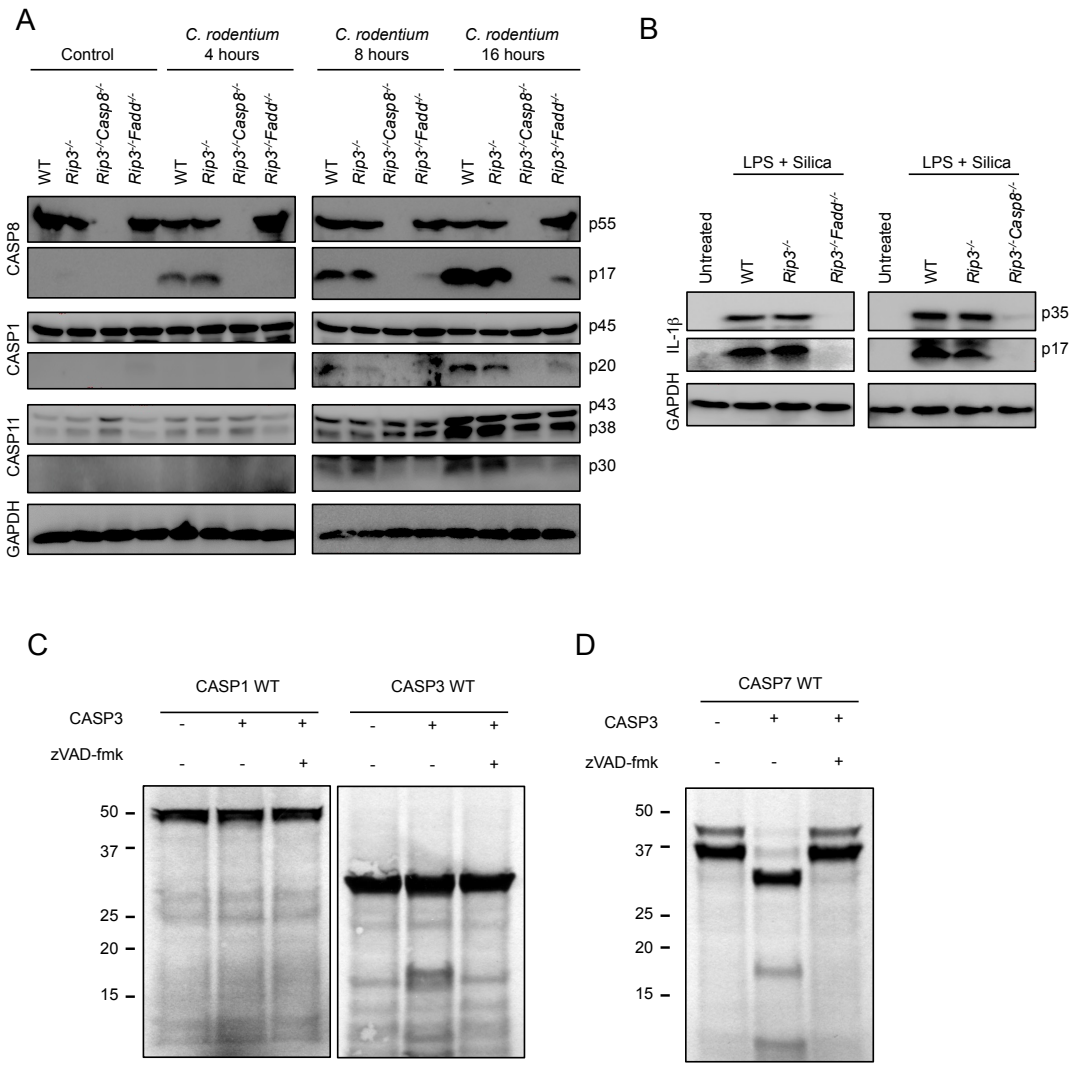
Supplemental Figure 1. Phenotypic and phagocytic analysis of *Rip3$^{-/-}$Casp8$^{-/-}$* and *Rip3$^{-/-}$Fadd$^{-/-}$* BMDMs. (**A-C**) WT, *Rip3$^{-/-}$Casp8$^{-/-}$* and *Rip3$^{-/-}$Fadd$^{-/-}$* BMDMs were visualized by light microscopy **(A)** and analyzed for surface expression of the myeloid/macrophage markers CD11b **(B)** and F4/80 **(C)** by flow cytometry. **(D)** WT, *Rip3$^{-/-}$Casp8$^{-/-}$* and *Rip3$^{-/-}$Fadd$^{-/-}$* BMDMs were either left untreated or stimulated with LPS (20ng/ml) for 24 hours before surface expression of CD86 was analyzed by flow cytometry. (**E-G**) WT, *Rip3$^{-/-}$Casp8$^{-/-}$* and *Rip3$^{-/-}$Fadd$^{-/-}$* BMDMs were infected with a GFP-expressing *C. rodentium* strain (Citrobacter-GFP) **(E)**, or incubated with FITC-labeled zymosan **(F)** or ovalbumin (OVA) **(G)** for 4 hours before uptake of these particles was determined by flow cytometry. Data are representative of at least 3 independent experiments.



Supplemental Figure 2. Canonical and non-canonical Nlrp3 inflammasome activation. (**A and B**) WT, *Rip3*$^{-/-}$, *Rip3*$^{-/-}$*Casp8*$^{-/-}$ and *Rip3*$^{-/-}$*Fadd*$^{-/-}$ BMDMs were either left untreated or stimulated with ATP for 30 minutes (**A, left**), LPS (20ng/ml) for 4 hours (**A, right**) or LPS (20ng/ml) for 3 hours followed by Silica 5 (500μg) for 5 hours (**B**). Cell lystates were then immunoblotted for the indicated proteins. **(C)** WT, *Casp11*$^{-/-}$ and *Casp1*$^{-/-}$*Casp11*$^{-/-}$ BMDMs were infected with *C. rodentium* or *E. coli* (m.o.i. 25) for 24 hours as described in Materials and Methods, and lysates were immunoblotted for the indicated proteins. **(D and E)** WT, *LysM-Cre*$^{+}$*-Casp8*$^{flox/flox}$, and *Rip3*$^{-/-}$*Casp8*$^{-/-}$ BMDMs were left untreated, stimulated with LPS+ATP, or infected with *C. rodentium* as described in Materials and Methods. Cell lysates were immunoblotted for caspase-8 and GAPDH. Data are representative of 3 independent experiments.



Supplemental Figure 3. TNF-α and TNFR1 are dispensable for both canonical and non-canonical Nlrp3 inflammasome activation. **(A-F)** WT, *TNF-α*$^{-/-}$ and *TNF-R1*$^{-/-}$ BMDMs were stimulated with 20ng/ml LPS for 4 hours **(A-C)**, the last 30 minutes of which in the presence of 5mM ATP or infected with *C. rodentium* for 24 hours **(D-F)**. Cell lysates were immunoblotted for caspases-1 and -8 (**A and D**), and culture supernatants were analyzed for IL-1β (**B, C, E and F**). Data show mean ± s.e.m., and are representative of 3 independent experiments.



Supplemental Figure 4. (A) Kinetic analysis of Nlrp3 inflammasome activation by *C. rodentium* infection. WT, *Rip3*$^{-/-}$, *Rip3*$^{-/-}$*Casp8*$^{-/-}$ and *Rip3*$^{-/-}$*Fadd*$^{-/-}$ BMDM cells were stimulated with 25 m.o.i. of *C. rodnetium* for 4, 8 and 16 hours. Cell lysates were analyzed for indicated proteins by western blot. Data are representative of two independent experiments. **(B) LPS+Silica-induced IL-1β cleavage in *Rip3*$^{-/-}$*Fadd*$^{-/-}$ BMDM.** WT, *Rip3*$^{-/-}$, *Rip3*$^{-/-}$*Casp8*$^{-/-}$ and *Rip3*$^{-/-}$*Fadd*$^{-/-}$ BMDMs were stimulated with LPS for 3 hours followed by Silica 5 (500μg) for 6 hours. Cell lysates were analyzed for IL-1β induction and cleavage by western blot. **(C and D) Cleavage of procaspase-3 and procaspase-7 by recombinant mouse caspase-3 *in vitro*. (C)** Procaspase-1 and procaspase-3 were produced *in vitro*, and incubated with recombinant caspase-3 (35ng) at 37˚C for 1 hour before procaspase-1 and -7 processing was analyzed by autoradiography. In some setups, caspase-3 was pre-incubated with 1μM zVAD-fmk prior to co-incubation with procaspase-1 and -3. **(D)** Wildtype procaspase-7 was produced *in vitro*, and incubated with recombinant caspase-3 (35ng) at 37˚C for 1 hour before procaspase-7 processing was analyzed by autoradiography. In some setups, caspase-3 was pre-incubated with 1μM zVAD-fmk prior to co-incubation with procaspase-7.